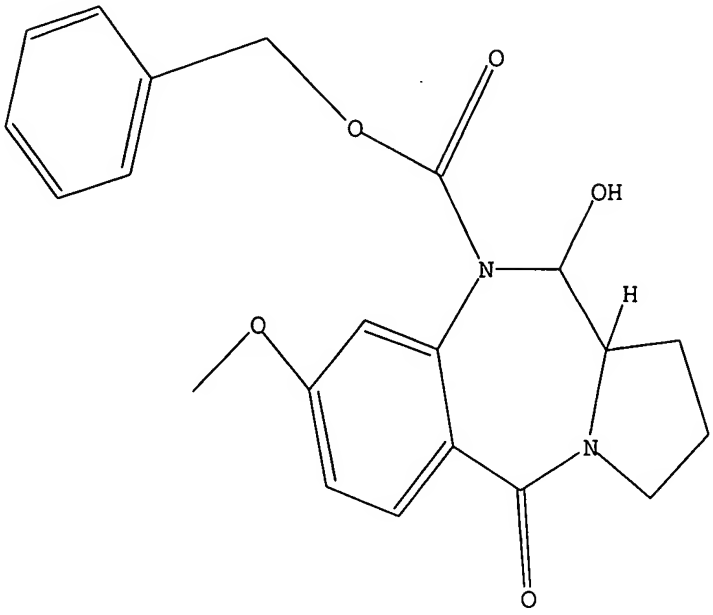
=>
Uploading C:\Program Files\Stnexp\Queries\10824743c.str

L3 STRUCTURE UPLOADED

=> d
L3 HAS NO ANSWERS
L3 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l3 full
FULL SEARCH INITIATED 12:32:38 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 93 TO ITERATE

100.0% PROCESSED 93 ITERATIONS 33 ANSWERS
SEARCH TIME: 00.00.01

L4 33 SEA SSS FUL L3

L5 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1251578 CAPLUS

DOCUMENT NUMBER: 144:150340

TITLE: Synthesis and biological evaluation of novel pyrrolo[2,1-c][1,4]benzodiazepine prodrugs for use in antibody-directed enzyme prodrug therapy

AUTHOR(S): Masterson, Luke A.; Spanswick, Victoria J.; Hartley, John A.; Begent, Richard H.; Howard, Philip W.; Thurston, David E.

CORPORATE SOURCE: CR-UK Gene Targeting Drug Design Research Group, School of Pharmacy, University of London, London, WC1 1AX, UK

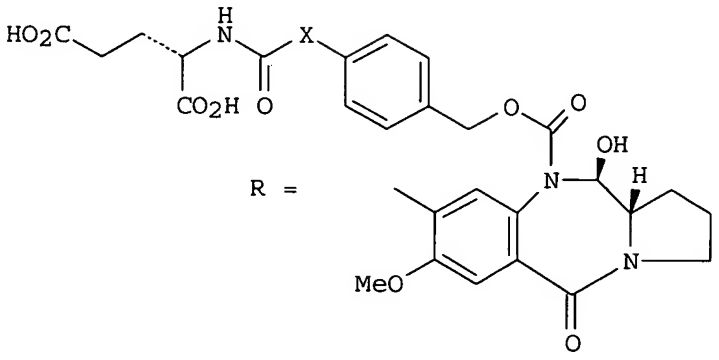
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(2), 252-256
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



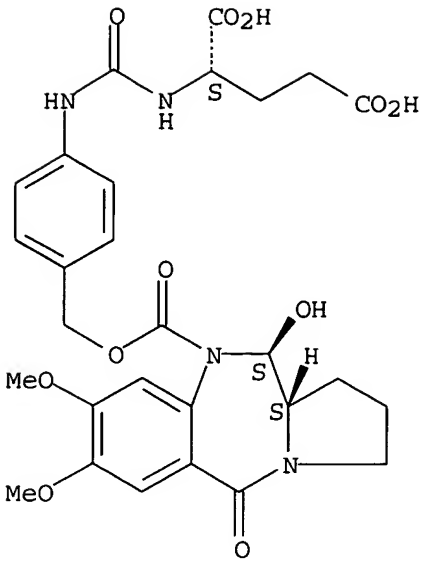
AB The design, synthesis and evaluation of four novel pyrrolo[2,1-c][1,4]benzodiazepine (PBD) prodrugs ROMe and RO(CH2)3OR [X = O, NH] for potential use in carboxypeptidase G2 (CPG2)-based antibody-directed enzyme prodrug therapy (ADEPT) is reported. Although all four prodrugs were shown to be less cytotoxic than the released parent PBDs, the urea prodrugs were found to be too unstable for use in ADEPT, whereas the carbamates are both stable in an aqueous environment and are good substrates for CPG2.

IT 848004-47-7P 848004-56-8P 848004-84-2P
848004-85-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and biol. evaluation of pyrrolo[2,1-c][1,4]benzodiazepine prodrugs for use in antibody-directed enzyme prodrug therapy)

RN 848004-47-7 CAPLUS

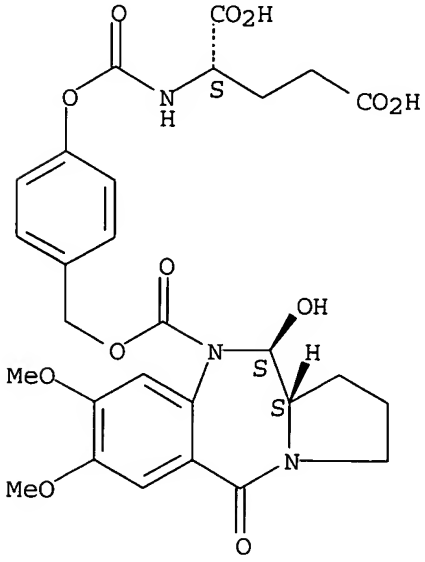
CN L-Glutamic acid, N-[[[4-[[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenyl]amino]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



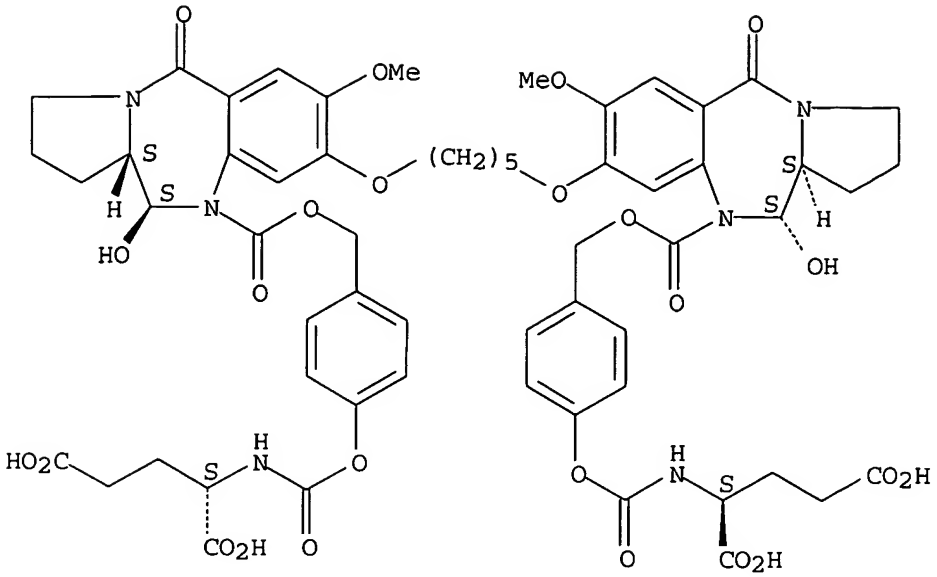
RN 848004-56-8 CAPLUS
CN L-Glutamic acid, N-[[4-[[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenoxy]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



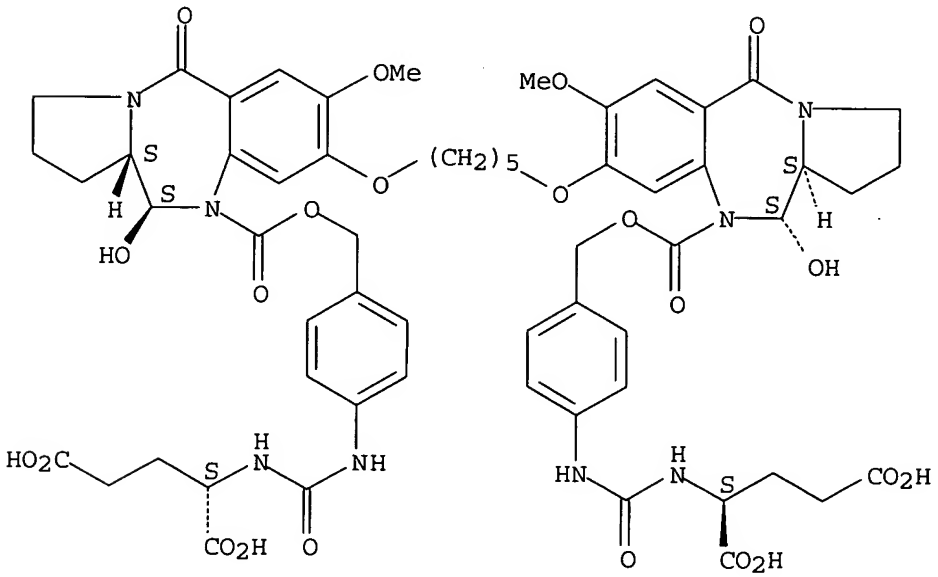
RN 848004-84-2 CAPLUS
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 848004-85-3 CAPLUS
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

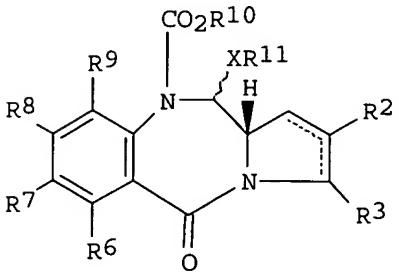
L5 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:238991 CAPLUS
DOCUMENT NUMBER: 142:316867
TITLE: Synthesis of protected pyrrolobenzodiazepines
INVENTOR(S): Howard, Philip; Masterson, Luke
PATENT ASSIGNEE(S): Spirogen Limited, UK
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

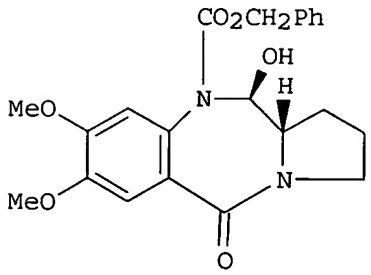
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005023814	A1	20050317	WO 2004-GB3873	20040910
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1664049	A1	20060607	EP 2004-768420	20040910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				

PRIORITY APPLN. INFO.: GB 2003-21295 A 20030911
WO 2004-GB3873 W 20040910

OTHER SOURCE(S): MARPAT 142:316867
GI



I



II

AB Pyrrolobenzodiazepines I [R2, R3 = H, O, OH, CH2, CN, R, OR, O3SR, COR; R = (un)substituted alkyl, heterocyclyl, aryl; R6, R7, R9 = H, R, OH, OR, SH, SR, NH2, NHR, NRR1, NO2, SnMe3, halogen; R1 = (un)substituted alkyl, heterocyclyl, aryl; R8 = H, R, OH, OR, SH, SR, NH2, NHR, NRR1, NO2, SnMe3, halogen, XR4X; R4 = alkylene, heteroalkylene; X = O, S, NH; CO2R10 = protective group; R11 = H, R] were prepared by treating an isocyanatobenzoate with an alc. to form the carbamate, followed by

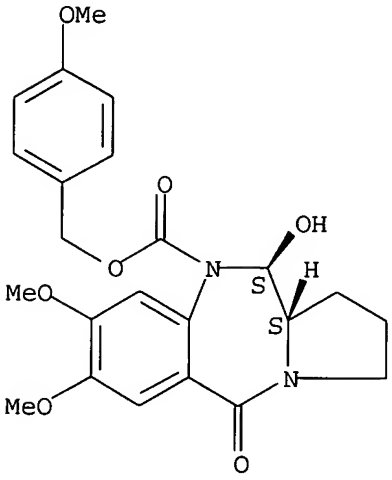
(S)-2-pyrrolidinemethanol, cyclizing, optionally alkylating the resulting OH group. Thus, 2,4,5-O2N(MeO)2C6H2CO2H was amidated with (S)-2-pyrrolidinemethanol, followed by tert-butyldimethylsilyl protection, reduction of the nitro group, and conversion of the amine to isocyanate. The isocyanate was treated with benzyl alc. to give the benzyloxycarboylamine which was desilylated and cyclized with base to give the pyrrolobenzodiazepine II.

IT 848004-38-6P 848004-41-1P 848004-46-6P
848004-54-6P 848004-56-8P 848004-82-0P
848004-83-1P 848004-84-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of protected pyrrolobenzodiazepines)

RN 848004-38-6 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, (4-methoxyphenyl)methyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

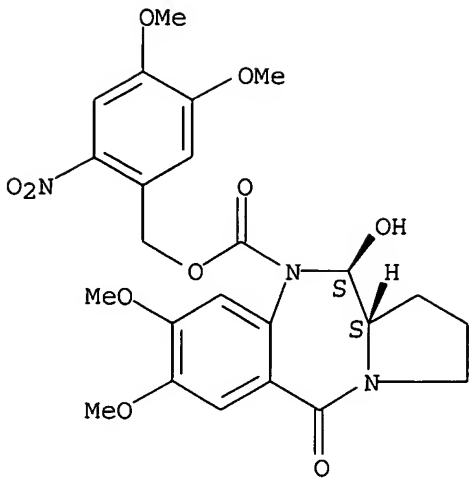
Absolute stereochemistry. Rotation (+).



RN 848004-41-1 CAPLUS

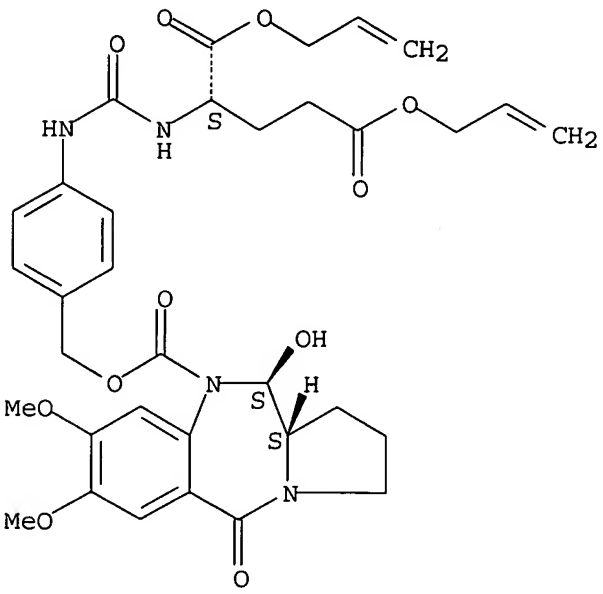
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



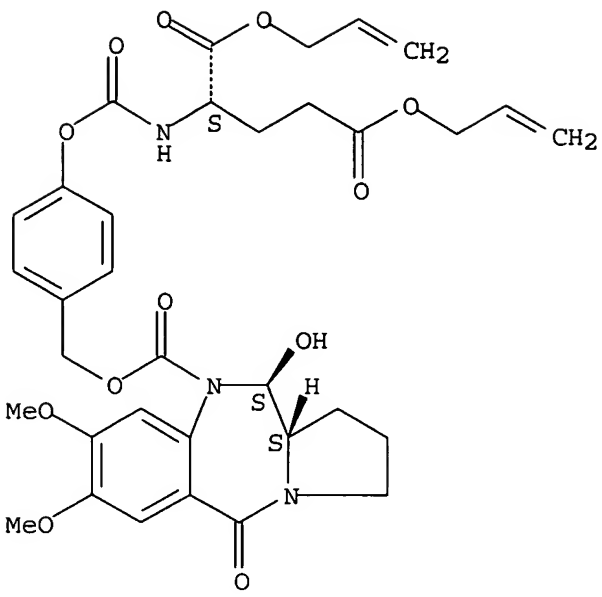
RN 848004-46-6 CAPLUS
CN L-Glutamic acid, N-[[[4-[[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenyl]amino]carbonyl]-, di-2-propenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



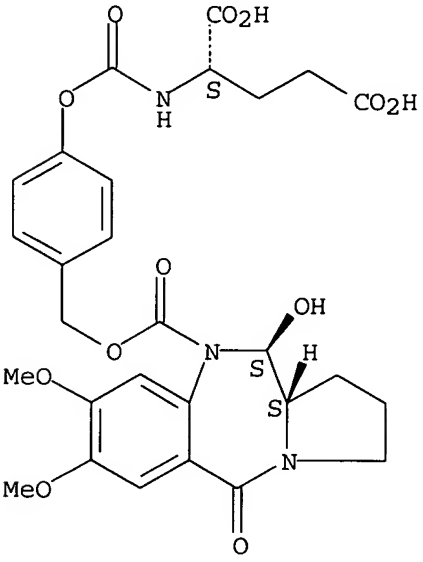
RN 848004-54-6 CAPLUS
CN L-Glutamic acid, N-[[4-[[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenoxy]carbonyl]-, di-2-propenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 848004-56-8 CAPLUS
CN L-Glutamic acid, N-[[4-[[[[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl]carbonyl]oxy]methyl]phenoxy]carbonyl]- (9CI) (CA INDEX NAME)

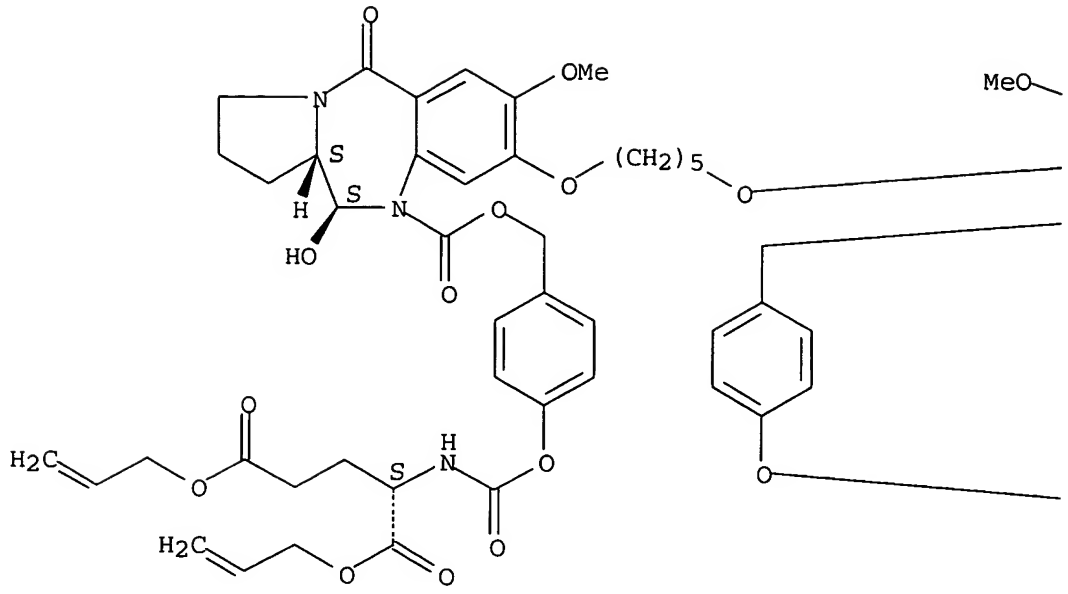
Absolute stereochemistry.



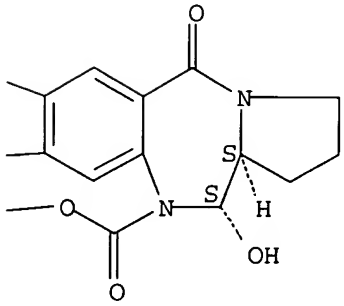
RN 848004-82-0 CAPLUS
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneoxycarbonyl]]bis-, tetra-2-propenyl ester (9CI) (CA INDEX NAME)

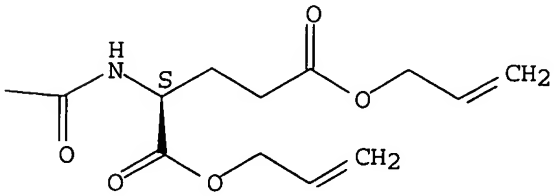
Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B

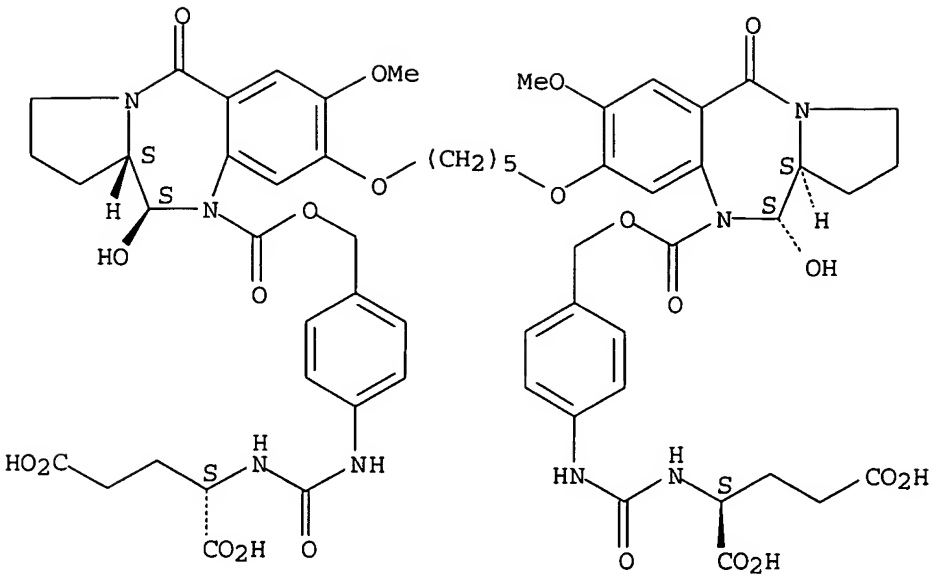




RN 848004-83-1 CAPLUS

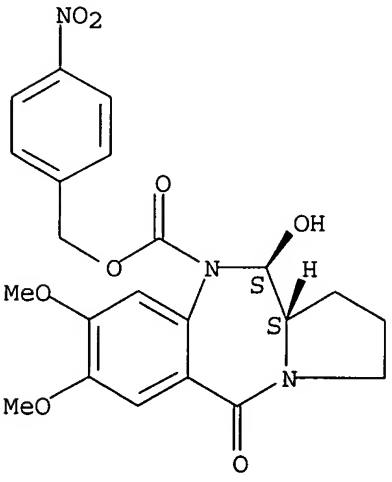
CN L-Glutamic acid, N,N'-[1,5-pentanediylbis[oxy[(11S,11aS)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8,10(5H)-diyl]carbonyloxymethylene-4,1-phenyleneiminocarbonyl]]bis-, tetra-2-propenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 848005-03-8 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, (4-nitrophenyl)methyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:619247 CAPLUS
DOCUMENT NUMBER: 133:362758
TITLE: Design and synthesis of novel pyrrolobenzodiazepine (PBD) prodrugs for ADEPT and GDEPT
AUTHOR(S): Sagnou, M. J.; Howard, P. W.; Gregson, S. J.; Eno-Amooquaye, E.; Burke, P. J.; Thurston, D. E.
CORPORATE SOURCE: School of Pharmacy and Biomedical Sciences, CRC Gene Targeting Drug Design Research Group, University of Portsmouth, Hants, PO1 2DT, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(18), 2083-2086

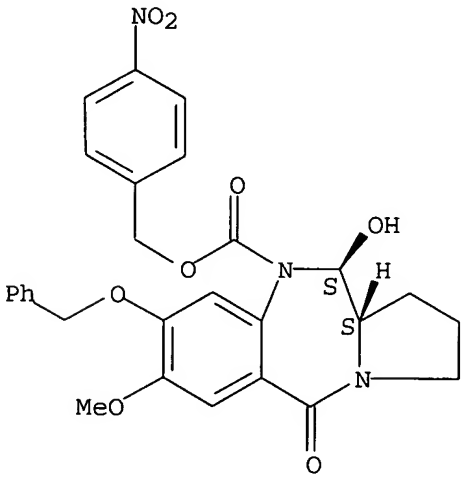
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:362758

AB Three N10-(4-nitrobenzyl)carbamate-protected PBD prodrugs were prepared and evaluated for potential use in nitro reductase-based ADEPT (antibody-directed enzyme chemotherapy) and GDEPT (gene-directed chemotherapy). For example, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-1H-pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid (4-nitrophenyl)methyl ester was prepared, which is a prodrug precursor to benzyl DC 81. An approx. 100-fold activation was observed for benzyl DC 81.

IT 307925-10-6P 307925-11-7P 307925-16-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrrolobenzodiazepine prodrugs for antibody-directed enzyme chemotherapy (ADEPT) and gene-directed enzyme chemotherapy (GEDEPT))

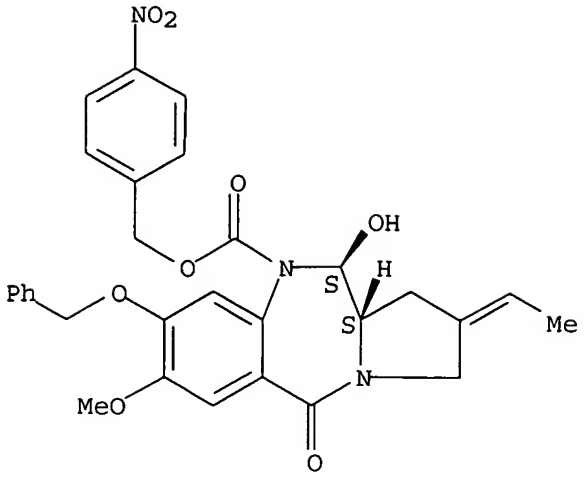
RN 307925-10-6 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4-nitrophenyl)methyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



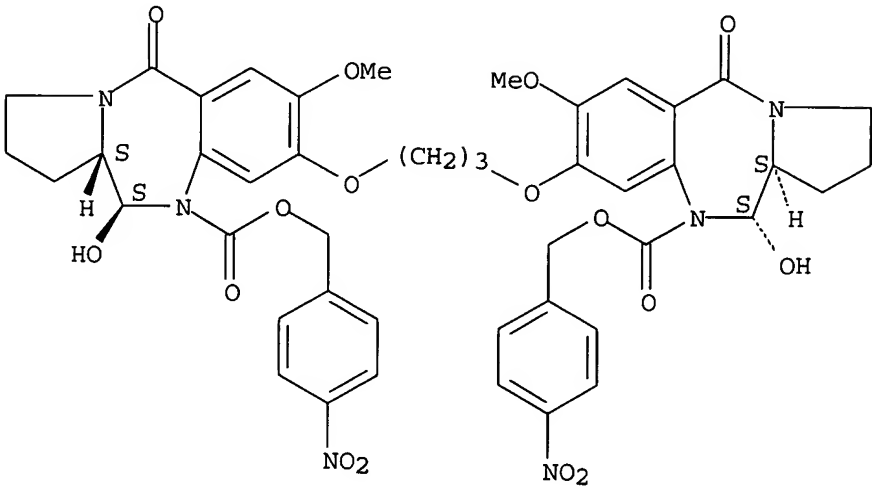
RN 307925-11-7 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2-ethylidene-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4-nitrophenyl)methyl ester, (11S,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 307925-16-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11S,11'S,11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:161285 CAPLUS
DOCUMENT NUMBER: 132:207852
TITLE: Solid-phase preparation and combinatorial libraries of pyrrolobenzodiazepine derivatives for drug screening
INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson
PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012509	A2	20000309	WO 1999-GB2839	19990827
WO 2000012509	A3	20000706		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2341386	AA	20000309	CA 1999-2341386	19990827
AU 9955262	A1	20000321	AU 1999-55262	19990827
AU 764464	B2	20030821		
EP 1107970	A2	20010620	EP 1999-941767	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525286	T2	20020813	JP 2000-571055	19990827
NZ 510489	A	20021126	NZ 1999-510489	19990827
US 6747144	B1	20040608	US 2001-763813	20010226
US 2004198722	A1	20041007	US 2004-824743	20040415
PRIORITY APPLN. INFO.:			GB 1998-18732 A	19980827
			WO 1999-GB2839 W	19990827
			US 2001-763813 A1	20010226

OTHER SOURCE(S): MARPAT 132:207852

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I are prepared [wherein: R = (un)substituted alk(en/yn)yl, aralkyl, aryl, or heteroat. analogs; R2 and R3 = H, R, OH, OR, O, :CHR, :CH2, CH2CO2R, CH2CO2H, CH2SO2R, OSO2R, CO2R, COR, and cyano; optionally double bond in ring; R6, R7, R8, and R9 = H, R, OH, OR, halo, NO2, amino, Me3Sn; or R7R8 = O(CH2)1-2O; R11 = H or R; Q = S, O, or NH; L = linking group or bond; Sup = solid support; or where 1 or more of R2, R3, R6, R7 and R8 = independently = H-(T)n-X-Y-A- where: X = CO, NH, S or O; T = combinatorial unit; Y = divalent group such that HY = R; A = O, S, NH, or bond; and n = pos. integer]. The compds. are intermediates for pyrrolobenzodiazepine derivs. II, which are claimed as being potentially useful for treatment of bacterial, parasitic, viral, and gene-based diseases. For example, the supported chloroformate ester III underwent (1) elaboration with 4,5-dimethoxyanthranilic acid, (2) amidation with 2-pyrrolidinemethanol, and (3) oxidative cyclization using SO3.pyridine and DMSO, to give the invention compound IV. Photochem. cleavage of IV gave the corresponding aminal, which was dehydrated in situ to give the corresponding compound V. The cleavage product showed cytotoxicity against human leukemia cells which was identical to that of authentic samples of V. Another compound I was derivatized at a sidechain using 3 amino acids in 3 chain positions to give a 27-member combinatorial library.

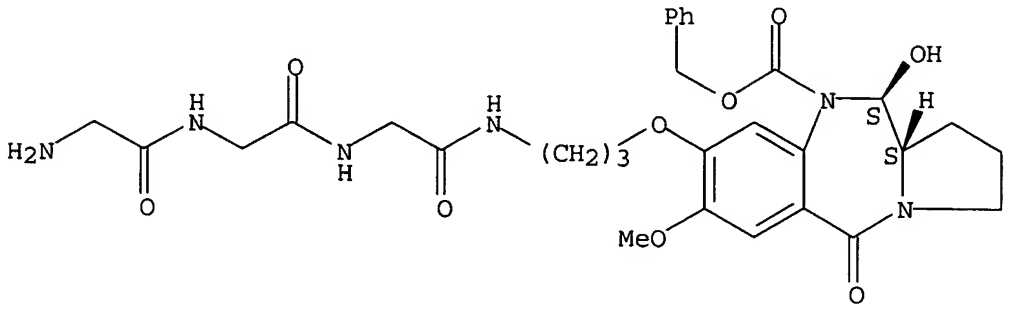
IT 260417-41-2DP, derivs.
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(combinatorial library; solid-phase preparation and combinatorial libraries of pyrrolobenzodiazepine derivs. for drug screening)

RN 260417-41-2 CAPLUS

CN Glycinamide, glycylglycyl-N-[3-[[(11R,11aR)-2,3,5,10,11,11a-hexahydro-11-hydroxy-7-methoxy-5-oxo-10-[(phenylmethoxy)carbonyl]-1H-pyrrolo[2,1-

c][1,4]benzodiazepin-8-yl]oxy]propyl]- (9CI) (CA INDEX NAME)

Relative stereochemistry.

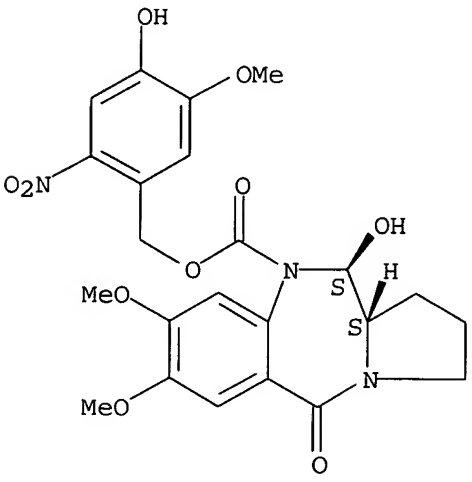


IT 260417-08-1DP, resin-bound 260417-22-9DP, resin-bound
260417-23-0DP, resin-bound 260417-25-2DP, resin-bound
260417-30-9DP, resin-bound 260417-35-4DP, resin-bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; solid-phase preparation and combinatorial libraries of pyrrolobenzodiazepine derivs. for drug screening)

RN 260417-08-1 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, (4-hydroxy-5-methoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

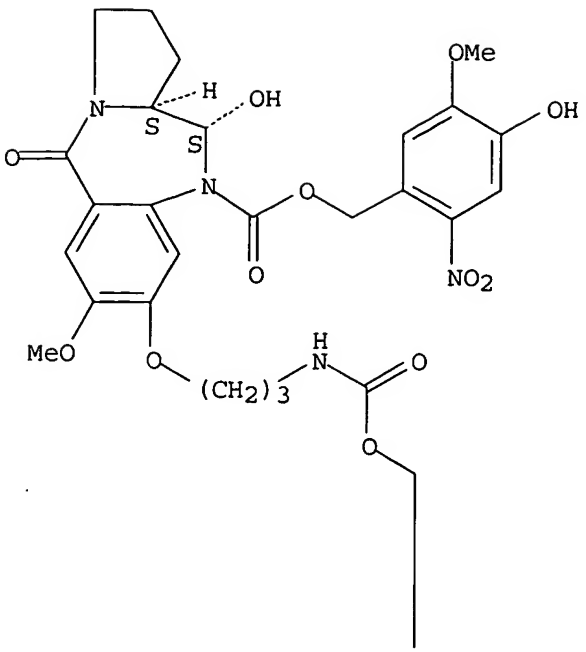


RN 260417-22-9 CAPLUS

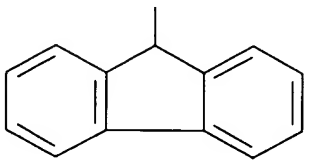
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, (4-hydroxy-5-methoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

PAGE 1-A

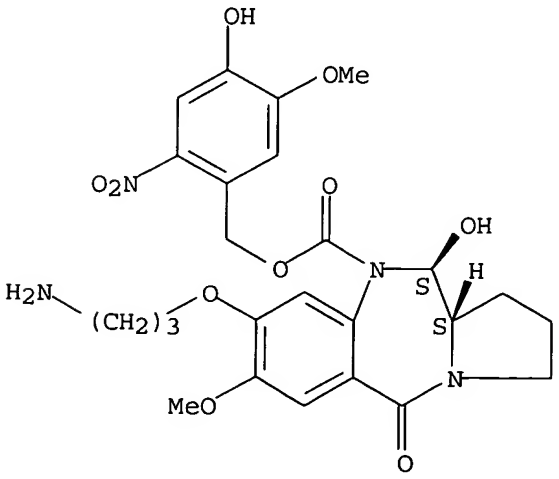


PAGE 2-A



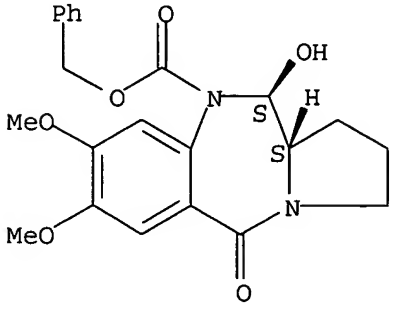
RN 260417-23-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(3-aminopropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, (4-hydroxy-5-methoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

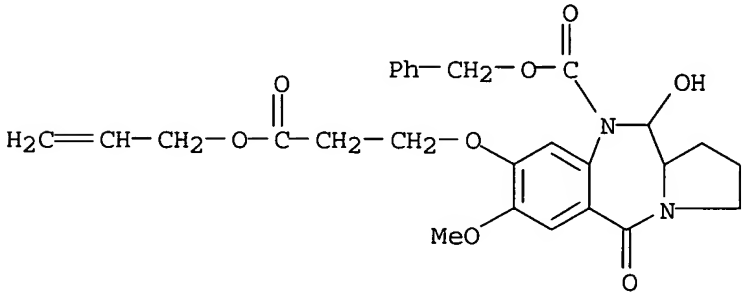


RN 260417-25-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7,8-dimethoxy-5-oxo-, phenylmethyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

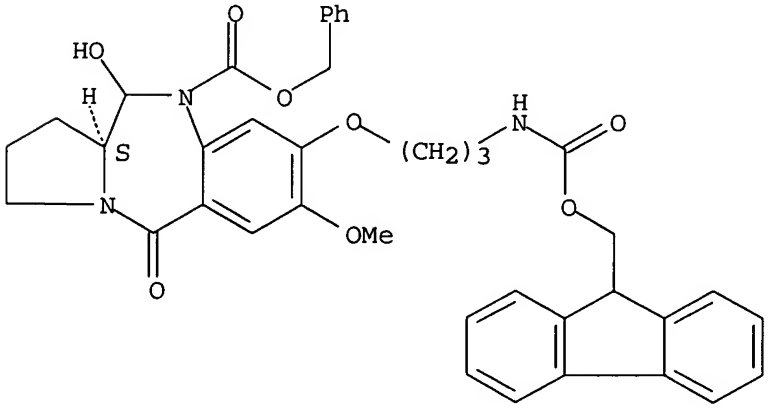


RN 260417-30-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, phenylmethyl ester (9CI) (CA INDEX NAME)



RN 260417-35-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, phenylmethyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

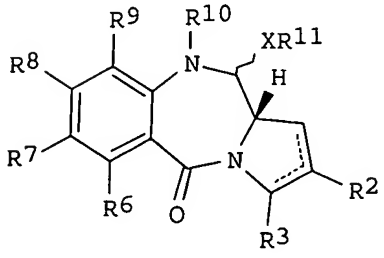


L5 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:161283 CAPLUS
DOCUMENT NUMBER: 132:207703
TITLE: Preparation of pyrrolobenzodiazepines (PBDs) as antitumor antibiotics
INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson
PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

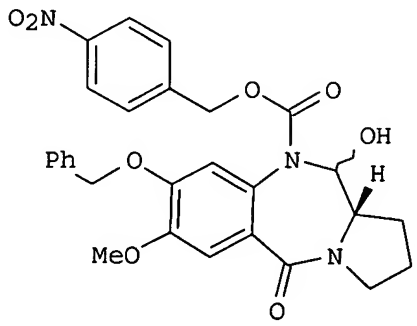
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012507	A2	20000309	WO 1999-GB2837	19990827
WO 2000012507	A3	20000831		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2341968	AA	20000309	CA 1999-2341968	19990827
AU 9955261	A1	20000321	AU 1999-55261	19990827
AU 758398	B2	20030320		
EP 1109811	A2	20010627	EP 1999-941766	19990827
EP 1109811	B1	20030806		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525284	T2	20020813	JP 2000-571053	19990827
AT 246687	E	20030815	AT 1999-941766	19990827
NZ 510492	A	20030829	NZ 1999-510492	19990827
PT 1109811	T	20031231	PT 1999-941766	19990827
ES 2205872	T3	20040501	ES 1999-941766	19990827
US 6562806	B1	20030513	US 2001-763814	20010226
US 2003195196	A1	20031016	US 2003-379049	20030304

PRIORITY APPLN. INFO.: GB 1998-18731 A 19980827
WO 1999-GB2837 W 19990827
US 2001-763814 A1 20010226

OTHER SOURCE(S): MARPAT 132:207703
GI



I



II

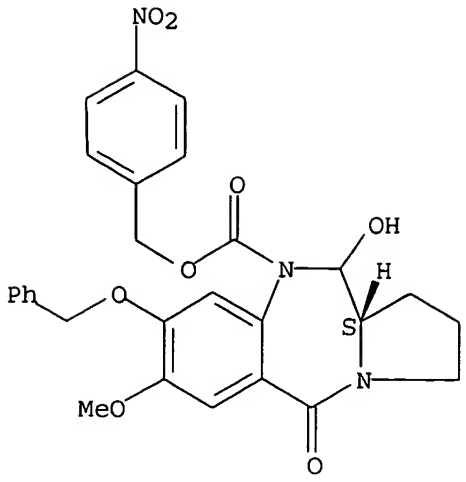
AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein R = (un)substituted (ar)alkyl, etc.; R2 and R3 = independently H, R, OH, OR, =O, =CH-R, =CH2, CH2-CO2R, CH2-CO2H, CH2-SO2R, O-SO2-R, CO2R, COR, or CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NO2, or Me3Sn; or R7 and R8 together form a -O-(CH2)p-O- group, where p = 1 or 2; or the compound is a dimer with each monomer being the same or different and being of formula I and the R8 groups of the monomers form a -T-R'-T- bridge, where R' is an alkylene chain which may contain ≥ 1 heteroatoms and/or aromatic rings and/or carbon-carbon double or triple bonds, and each T = independently O, S, or N; R10 = a therapeutically removable N-protecting group; R11 = H or R; X is S, O, or NH] were prepared for the treatment of cancer and other site-specific diseases where a local increase of toxicity is beneficial to the patient. Examples include the syntheses of benzyl DC-81, benzyl tomaymycin, and DSB-120 prodrugs starting from 2-nitrobenzoic acid derivs. and pyrrolidines. Data from enzyme and light activation studies and cytotoxicity assays are also given. For example, the nitroreductase-activated benzyl DC-81 (II) was formed in a 6-step sequence involving: (1) benzylation of vanillic acid (67%); (2) ring nitration (82%); (3) amidation with (2S)-pyrrolidinemethanol (88%); (4) reduction of the nitro group (81%); (5) N-addition of 4-nitrobenzyl chloroformate; and (6) cyclization using Swern oxidation conditions (31%). In the presence of nitroreductase and the NADH co-factor, II demonstrated antitumor activity (IC50 = 1-5 μM) against the SW1116 and LS174T human adenocarcinoma colonic cell lines. II proved non-toxic in SW1116 cells at concns. ≤ 500 μM and showed slight toxicity in LS174T cells at concns. > 100 μM. I may also be suitable for treating bacterial, parasitic, or viral infections by exploiting a unique enzyme produced at the site of infection which is not natural to the host, or by exploiting an elevation in the amount of an enzyme which does occur naturally in the host.

IT 260391-39-7P 260391-41-1P 260391-42-2P
260391-43-3P 260391-44-4P 260391-45-5P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compound; preparation of pyrrolobenzodiazepinone prodrugs from 2-nitrobenzoic acid derivs. and pyrrolidines for the treatment of cancer)

RN 260391-39-7 CAPLUS

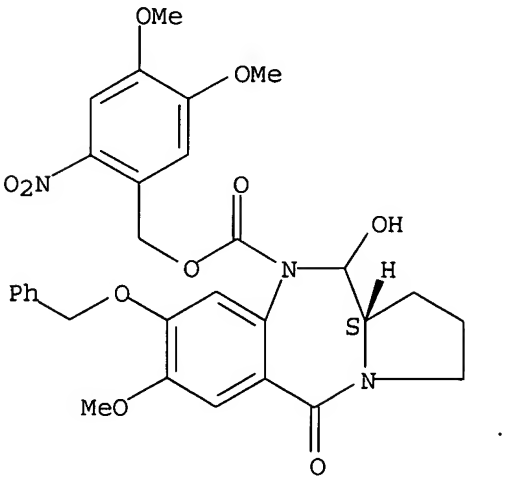
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4-nitrophenyl)methyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



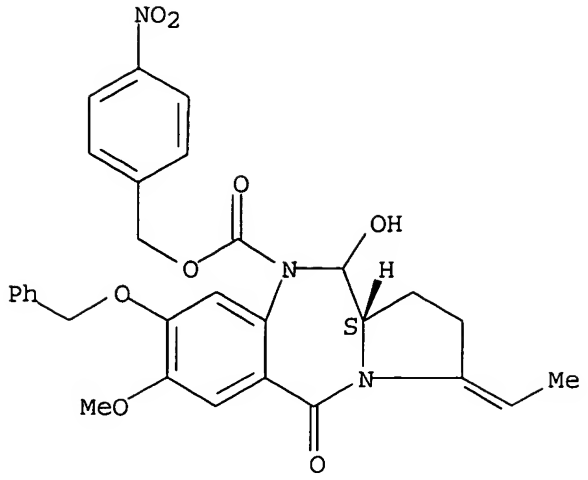
RN 260391-41-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



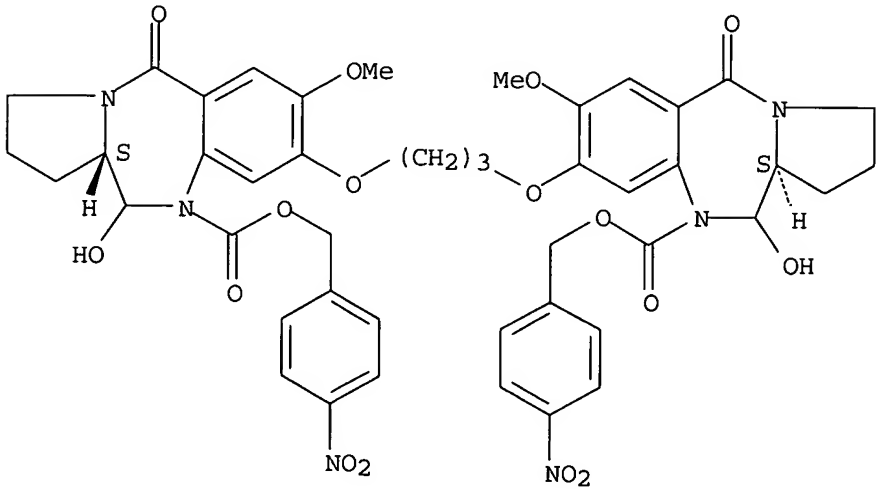
RN 260391-42-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 3-ethylidene-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-(phenylmethoxy)-, (4-nitrophenyl)methyl ester, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



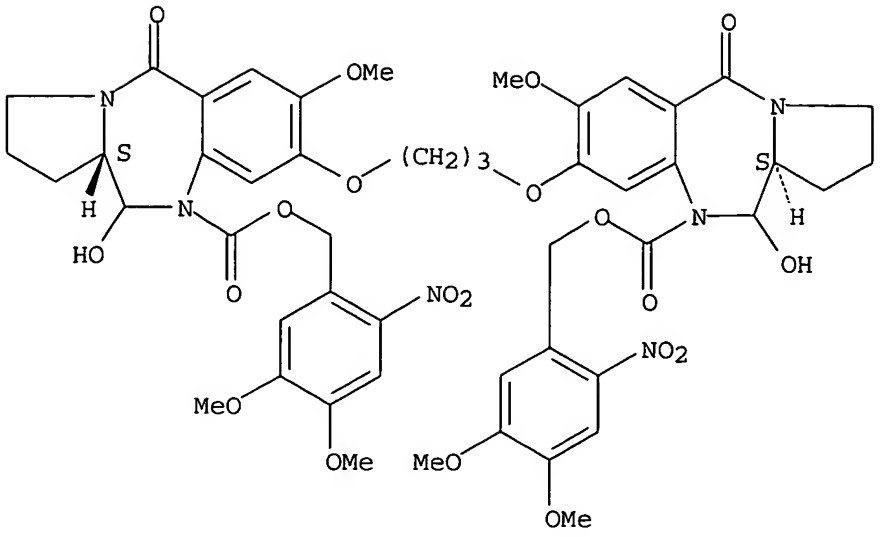
RN 260391-43-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4-nitrophenyl)methyl] ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



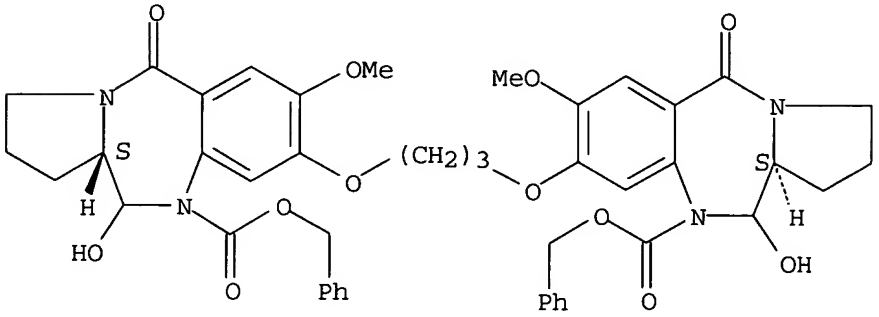
RN 260391-44-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis[(4,5-dimethoxy-2-nitrophenyl)methyl] ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 260391-45-5 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, bis(phenylmethyl) ester, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:161282 CAPLUS
DOCUMENT NUMBER: 132:208134
TITLE: Preparation of peptidyl pyrrolobenzodiazepines as pharmaceuticals
INVENTOR(S): Thurston, David Edwin; Howard, Philip Wilson
PATENT ASSIGNEE(S): The University of Portsmouth Higher Education Corporation, UK
SOURCE: PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012506	A2	20000309	WO 1999-GB2836	19990827
WO 2000012506	A3	20000629		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2341434	AA	20000309	CA 1999-2341434	19990827
AU 9955260	A1	20000321	AU 1999-55260	19990827
AU 763214	B2	20030717		
EP 1107969	A2	20010620	EP 1999-941765	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525283	T2	20020813	JP 2000-571052	19990827
NZ 510490	A	20031031	NZ 1999-510490	19990827
US 6608192	B1	20030819	US 2001-763768	20010226
US 2004092736	A1	20040513	US 2003-602521	20030624
PRIORITY APPLN. INFO.:			GB 1998-18730 A	19980827
			WO 1999-GB2836 W	19990827
			US 2001-763768 A1	20010226

OTHER SOURCE(S): MARPAT 132:208134
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Benzodiazepines I [X = CO2H, NH2 or protected amino, SH, OH; A = O, S, NH, or a single bond; R2, R3 = H, R, OH, OR, :O, :CHR, :CH2, CH2CO2R, CH2CO2H, CH2SO2R, OSO2R, CO2R, COR, CN, where R = alkyl, alkenyl, alkynyl, aralkyl, (un)substituted aryl; there is optionally a double bond between C1 and C2 or C2 and C3; R6, R7, R9 = H, R, OH, OR, halo, nitro, amino, Me3Sn; R11 = H or R; Q = S, O or NH; R10 is a nitrogen-protecting group; Y is a divalent group such that HY = R] were prepared and incorporated into peptides for use as pharmaceuticals. Thus, pyrrolo[2,1-c][1,4]benzodiazepine derivative II (Fmoc = fluorenylmethoxycarbonyl) was prepared and applied to the synthesis of a 27-member glycine/valine/phenylalanine tripeptide library which was screened for inhibition of leukemia cells.

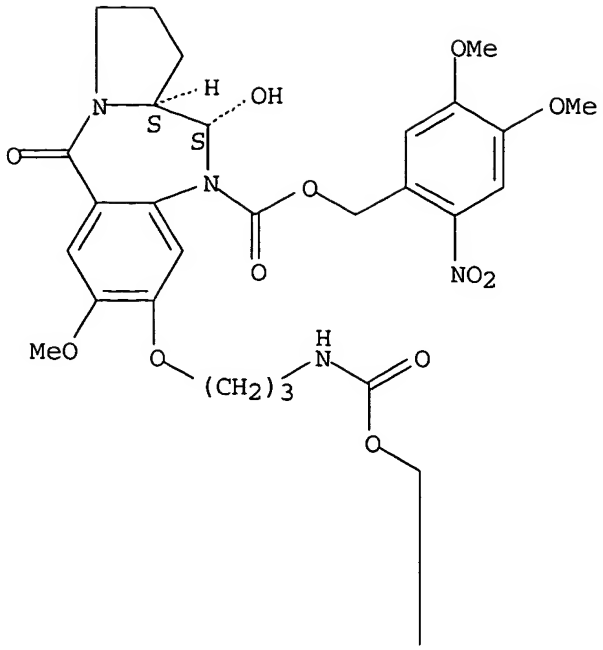
IT 260449-57-8P 260449-60-3P 260449-61-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptidyl pyrrolobenzodiazepines as pharmaceuticals)

RN 260449-57-8 CAPLUS

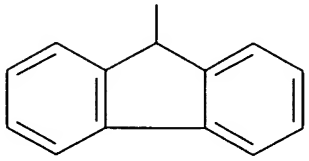
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-[3-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]propoxy]-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

PAGE 1-A

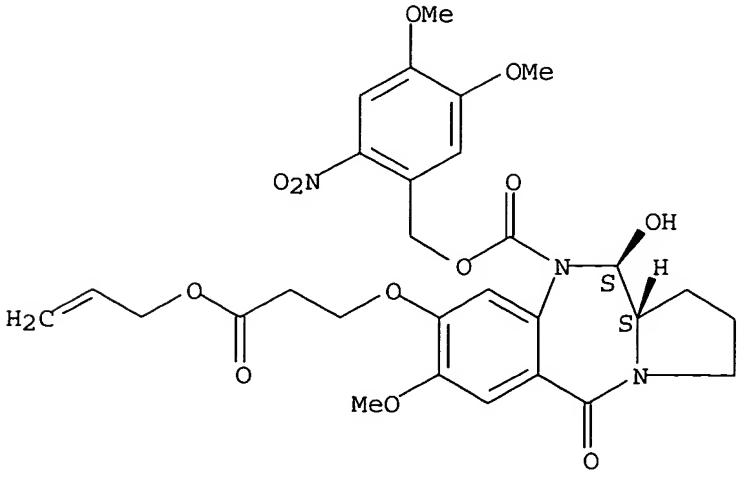


PAGE 2-A



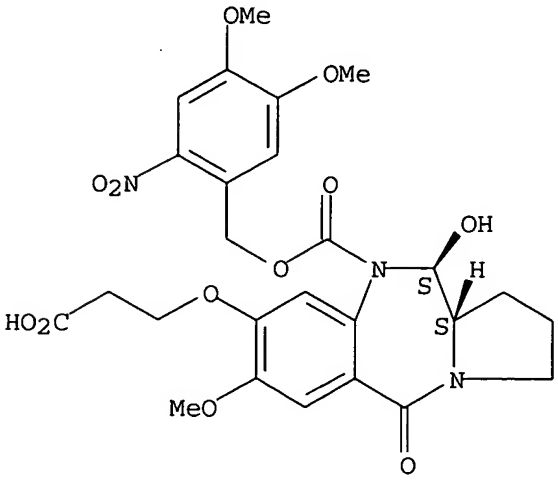
RN 260449-60-3 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-8-[3-oxo-3-(2-propenyloxy)propoxy]-, (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 260449-61-4 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(2-carboxyethoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, 10-[(4,5-dimethoxy-2-nitrophenyl)methyl] ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT 260449-58-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of peptidyl pyrrolobenzodiazepines as pharmaceuticals)
RN 260449-58-9 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-10(5H)-carboxylic acid, 8-(3-aminopropoxy)-2,3,11,11a-tetrahydro-11-hydroxy-7-methoxy-5-oxo-, (4,5-dimethoxy-2-nitrophenyl)methyl ester, (11R,11aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.